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Original research article

In vivo release of levonorgestrel from Sino-implant (II) — an innovative comparison of explant data☆,☆☆

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Abstract

Objectives: Measuring the amount of progestin remaining in contraceptive implants used for different lengths of time provides useful information on in vivo release kinetics including change over time. We compared estimated in vivo levonorgestrel (LNG) release rates derived from Sino-implant (II) explants with similar data from removed Jadelle.

Study design: We measured LNG remaining in 44 sets of Sino-implant (II) used for up to 7 years and removed in four Chinese clinics. Results were compared with published data for Jadelle explants used for up to 36 months. We estimated and compared monthly and daily LNG release rates for the two products using prediction models for drug release. We also estimated the dissolution profile similarity factor, f_2, for LNG release.

Results: Both Sino-implant (II) and Jadelle release approximately 30% of total LNG load after 3 years. Results of fitting the data to a biologically plausible modified Higuchi prediction model indicate comparable release through 3 years. An estimated similarity factor of 80.6 (90% confidence interval: 70.8–85.7) indicates similarity in the dissolution profiles of the two implants.

Conclusions: LNG release in vivo measured through explant analysis suggest that Sino-implant (II) and Jadelle may perform similarly through 3 years of use and could remain highly effective beyond this time point. These results align with published data for Jadelle and Sino-implant (II) showing high effectiveness for 5 years. Ongoing clinical studies comparing the products over 5 years present an opportunity to verify this supportive measure of clinical effectiveness.

Implications: This innovative approach provides evidence that Sino-implant (II) may perform clinically similarly to Jadelle over 3 years and remain a highly effective contraceptive beyond this time point. Data from explant analyses show promise for investigating the equivalence of elusion profiles of contraceptive implants.

Keywords: Sino-implant (II); Contraceptive implant; Explant; Jadelle; China

1. Introduction

The subdermal contraceptive implant Sino-implant (II) has been used by more than seven million women since its introduction in 1996 and is currently registered for use in more than 25 countries. Just like the implant system Jadelle, Sino-implant (II) consists of two Silastic® rods each containing 75 mg of levonorgestrel (LNG) (150 mg total). Four randomized trials conducted in China with more than 15,000 women assigned to Sino-implant (II) had first-year probabilities of pregnancy of nearly 0%. Cumulative probabilities of pregnancy during the 4 years of the product's approved duration of use were 0.9% and 1.06% in the two trials that presented data for 4-year use [1]. These annual pregnancy rates place Sino-implant (II) in the category of "highly effective contraceptive methods" with annual pregnancy rates between 0.0% and 0.9% per World Health Organization (WHO) definition [2] along with other implants, intrauterine devices and sterilization. While these effectiveness data are compelling, they are not sufficient for stringent regulatory approval of Sino-implant (II) primarily because the clinical trials from which they come were

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performed before modern good clinical practice (GCP) criteria were defined [3].

Currently, two GCP-compliant clinical studies in the Dominican Republic and China are under way to support an application for WHO prequalification of Sino-implant (II). While this regulatory path does not involve making the claim that Sino-implant (II) is a generic of the innovator product Jadelle, evaluating the similarity of the two products is a goal of the research since Jadelle is known to be a highly effective method.

FHI 360 has pursued two alternative approaches for assessing the similarity of Sino-implant (II) and Jadelle. First, in the ongoing clinical trials in the Dominican Republic and China, the clinical performance of Sino-implant (II), along with measures of total LNG concentrations and sex-hormone binding globulin, will be compared to Jadelle over 5 years of use. Second, we have evaluated the release rate of LNG in vivo from Sino-implant (II) and used appropriate statistical techniques to compare the rate to that of Jadelle [4]. Initial results of the latter approach are presented here.

2. Materials and methods

2.1. Sample

Sino-implant (II) explants were obtained from an evaluation of implant removal techniques at four Chinese clinics in 2008 [5]. Use duration was determined using clinic records and self-reported length of use in months documented at the time of removal. The explants were stored in sealed plastic bags at room temperature and tested at SGS Laboratories, a Swiss-based global service organization specializing in product inspection, testing, certification and verification in Shanghai, China. In early 2010, 44 sets of explant rods from this sample that had been used for 1 to 84 months were selected for analysis. Explants were selected from three clients (two rods from the same client) who had used the implants for the following lengths of time: 1, 6, 12, 18, 24, 36, 42/43, 48, 55, 60, 71/72 and 84 months, resulting in a total of 36 explant sets. Eight additional sets of implants that had been used to evaluate an LNG content assay developed for lot release testing of Sino-implant were added to the data set to increase statistical power. The explants were rinsed following a contraceptive implant decontamination procedure developed by the University of North Carolina Infectious Disease Laboratory involving submerging the explants in a 10% chlorine bleach/water solution for 10 min at room temperature, rinsing the explants in distilled water and drying at room temperature. The cleaning protocol had previously been shown to not affect the accuracy and precision of the LNG assay.

2.2. Measurement of LNG

Procedures for testing single explants for LNG content were based on a publically available analysis standard approved by the China State Pharmacopoeia Commission and originally developed for lot release testing of new implants [6]. FHI 360 previously validated this method for newly manufactured implants as part of the WHO prequalification process and subsequently validated it for explants. In brief, explants were cut into small fragments (~1-mm lengths), submerged in 10 mL of chloroform (reagent grade; TEDIA Company) for at least 3 h and then diluted with ethanol (absolute; Sinopharm Chemical Reagent Co.) to a 100-mL volume. Two sequential dilutions with ethanol (each with diluting 5 mL of the previous solution to 50 mL) were conducted to yield a final theoretical concentration of 0.0075 mg/mL LNG based on a 75-mg/rod initial level of LNG before insertion. With UV spectroscopy (UV-Shimadzu-2450PC), absorbance was determined at 240 nm (1-cm path length using a quartz cuvette) from the average of three replicate spectra. LNG content of the sample was calculated based on the absorbance of a LNG standard (National Institute for Food and Drug Control in China) determined under the same conditions. An LNG standard curve was prepared with eight standard concentrations ranging from 0.0008 to 0.0090 mg/mL of LNG in ethanol, containing 0.1% (v/v) chloroform. Accuracy was considered compliant if recovery for each sample was found to be within 98%–102%. Precision was considered compliant if the percent relative standard deviation (% RSD) for each solution is less than 2. For LNG levels ranging from 10% (0.0008 mg/mL) to 120% (0.009 mg/mL) of the label claim, the accuracy of the test method was found to be within 98.4%–101.5% recovery, while the precision ranged from 0.1% to 2.0% RSD. The average of the LNG content measurement at each time point was calculated for single rod explants.

We compared mean release rates for the observed Sino-implant (II) data over 3 years of use to publicly available data for 263 Jadelle explants which are reported in 100-day intervals over 3 years using the manufacturer's proprietary assay not in the public domain [7,8]. We then used the data for Sino-implant (II) to calculate release curves over the same period as that reported for Jadelle.

2.3. Statistical analysis

We considered two models for predicting mean LNG release over time:

$$\text{loss} = \alpha(\text{days})^{0.45}$$

and

$$\text{loss} = \alpha + \beta_1(\text{days})^{0.5} + \beta_2 \cdot \text{days}.$$

The first is a biologically plausible, modified Higuchi model [9] with zero intercept (i.e., 0% release at day zero) where the exponent of days (0.45) is determined based on the geometry of diffusion from a cylinder [10]. The second model was previously used by investigators at the Population Council when summarizing performance of Jadelle [8] and

Table 1
Cumulative mean and percent LNG released per set of explants.

	Jadelle			Sino-implant (II)		
Days of use	*N*	Mean mg (SD)	% Released	*N*	Mean mg (SD)	% Released
1–100	20	8.7 (6.7)	5.8	4	9.1 (2.1)	6.0
101–200	32	14.0 (8.8)	9.3	3	18.3 (7.0)	12.2
201–300	35	20.3 (5.1)	13.5	1	17.0 (NA)	11.3
301–400	25	22.6 (9.4)	15.1	4	25.0 (2.4)	16.6
401–500	22	27.2 (6.3)	18.8	–	–	–
501–600	29	30.6 (5.7)	20.4	4	30.8 (3.3)	20.5
601–700	32	32.7 (7.3)	21.8	–	–	–
701–800	26	32.9 (5.1)	21.9	4	36.8 (5.4)	24.5
801–900	16	43.3 (4.4)	28.9	–	–	–
901–1000	16	43.7 (3.7)	29.1	–	–	–
1001–1100	5	48.6 (3.6)	32.4	4	43.2 (3.5)	28.8
1101–1200	5	49.7 (4.2)	33.1	–	–	–
1201–1300	–	–	–	2	45.4 (1.0)	30.3
1401–1500	–	–	–	3	48.5 (11.4)	32.3
1601–1700	–	–	–	4	51.1 (2.7)	34.1
1801–1900	–	–	–	5	57.7 (7.0)	38.0
2101–2200	–	–	–	3	60.5 (4.2)	40.3
2501–2600	–	–	–	3	74.7 (0.7)	49.8

includes additional parameters corresponding to a nonzero intercept and a nonzero asymptotic LNG release rate. We fit each model using weighted least squares applied to interval midpoints on data collected through day 1100 (the overlapping range of available data for the two implants). We also estimated the release of LNG *per day* by taking the derivative of the release functions with respect to time, as follows:

$$\frac{dl}{dt} = 0.45 \cdot \alpha(\text{days})^{-0.55}$$

and

$$\frac{dl}{dt} = 0.5\beta_1(\text{days})^{-0.5} + \beta_2,$$

where β_2 corresponds to the asymptotic release rate of LNG under the model previously used by the Population Council.

In addition, we compared the rates of LNG release over time by estimating the similarity factor, f_2, a value commonly used to compare two dissolution profiles [4,11].

This factor is estimated as

$$\hat{f}_2 = 50 \cdot \log_{10}\left\{\left[1 + (1/p)\sum_{i=1}^{p}(\overline{x}_{ti} - \overline{x}_{ri})^2\right]^{-\frac{1}{2}} \cdot 100\right\},$$

where $\overline{x}_{ti}$ and $\overline{x}_{ri}$ are the average percent release values at time point i for the test [i.e., Sino-implant (II)] and reference (i.e., Jadelle) products, respectively, and p is the number of time points selected. The statistic takes the value 100 if there is perfect agreement between test and reference, with a lower limit of 0. Although subjective, values of f_2 between 50 (corresponding to an average difference of 10% in percent release across time) and 100 (perfect agreement in release profiles) indicate similarity between two dissolution profiles, which provides evidence to support the possible bioequivalence of the two products [11]. Though the f_2 factor is not used as a substitute for a bioequivalence study for a new product, it is reasonable to use the measure to compare ex vivo release profiles with extended-release products. For the explant data described here, the estimation of f_2 was restricted to the six intervals of time where at least two observations were available for each implant method (days 1–100, 101–200, 301–400, 501–600, 701–800 and 1001–1100).

3. Results

The mean LNG release data for Jadelle and Sino-implant (II) at 100-day use intervals suggest comparable release through 3 years (Table 1). Between 701 and 800 days, or about 2 years, Sino-implant (II) and Jadelle had released approximately 24.5% and 21.9% of the LNG, respectively. After 7 years of use, half of the LNG remained in the Sino-implant (II) samples. The release curves are comparable for Sino-implant (II) and Jadelle implants through year 3 based on the modified Higuchi model (Fig. 1a), with an estimated 42.9 mg of LNG (28.6% of the initial load) lost by year 3 among Sino-implant (II) users [95% confidence interval (CI): 41.2–44.5 mg] and 41.9 mg (27.9% of the initial load) for Jadelle users (95% CI: 39.4–44.3 mg). There was greater apparent discrepancy in predicted release curves between implant types when fitting the Population Council model (Fig. 1b), although the cumulative release through year 3 was not statistically significant between implant types: 44.1 mg released (95% CI: 41.5–48.6 mg) among Sino-implant (II) users and 47.6 mg released (95% CI: 43.6–51.5) among Jadelle users ($p = .161$). We also estimated a similarity factor (f_2) of 80.6 (90% CI: 70.8–85.7), indicative of

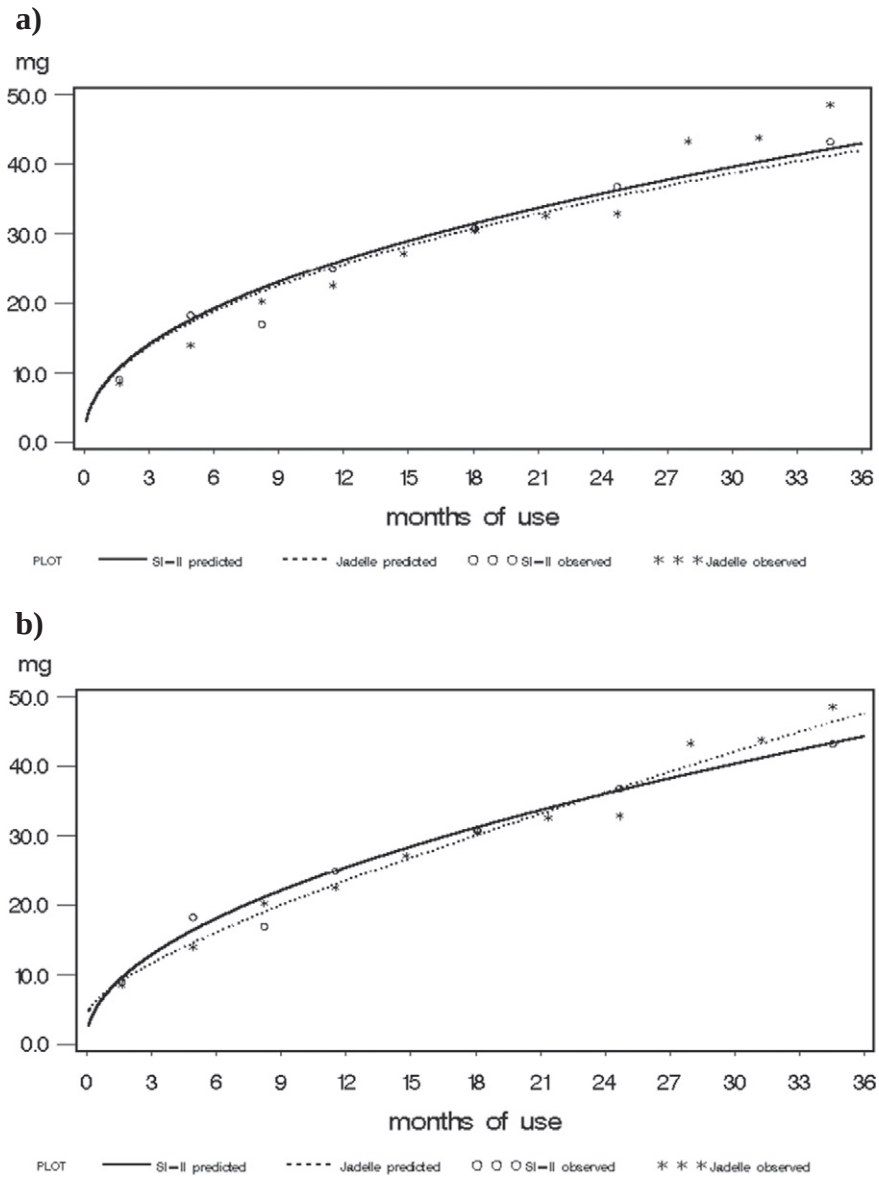

Fig. 1. (a) LNG released over 3 years estimated using a modified Higuchi model. (S-I (II): $Q = 1.838*\text{days}^{0.45}$; Jadelle: $Q = 1.796*\text{days}^{0.45}$). (b) LNG released over 3 years estimated using the Population Council model. (S-I (II): $Q = 0.412 + 1.29*\text{days}^{0.5} + 0.00094*\text{days}$; Jadelle: $Q = 3.509 + 0.647*\text{days}^{0.5} + 0.0207*\text{days}$).

substantial agreement between the percent release profiles of the two products.

For predicted daily LNG release rates, the modified Higuchi model (Fig. 2a) shows substantial agreement between Sino-implant (II) and Jadelle. Estimated daily release rates at year 2 are 22.0 mcg/day (95% CI: 21.2–22.9) and 21.5 mcg/day (95% CI: 20.2–22.8), respectively, for Sino-implant (II) and Jadelle users, while at year 3, the corresponding rates are 17.6 mcg/day (95% CI: 16.9–18.3) and 17.2 mcg/day (95% CI: 16.2–18.2). Results of fitting the Population Council model (Fig. 2b) suggest higher daily release rates for Jadelle than Sino-implant (II) at year 2 (32.6 mcg/day versus 24.8 mcg/day; p = .084) and year 3 (30.4 ng/day versus 20.4 ng/day; p = .110), but the differences were not statistically significant. The release rates for both products appear to level off and remain relatively stable between year 1 and year 3, regardless of model fit to the data. Given the relative "flatness" of the curves and previously established release kinetics for Jadelle showing steady release through 5 years [12], it is not unreasonable to assume that the trend would continue for Sino-implant (II).

4. Discussion

The results of this explant analysis indicate that Sino-implant (II) and Jadelle release LNG at similar rates through 3 years of use and, therefore, should have similar contraceptive effectiveness over this period. The modified

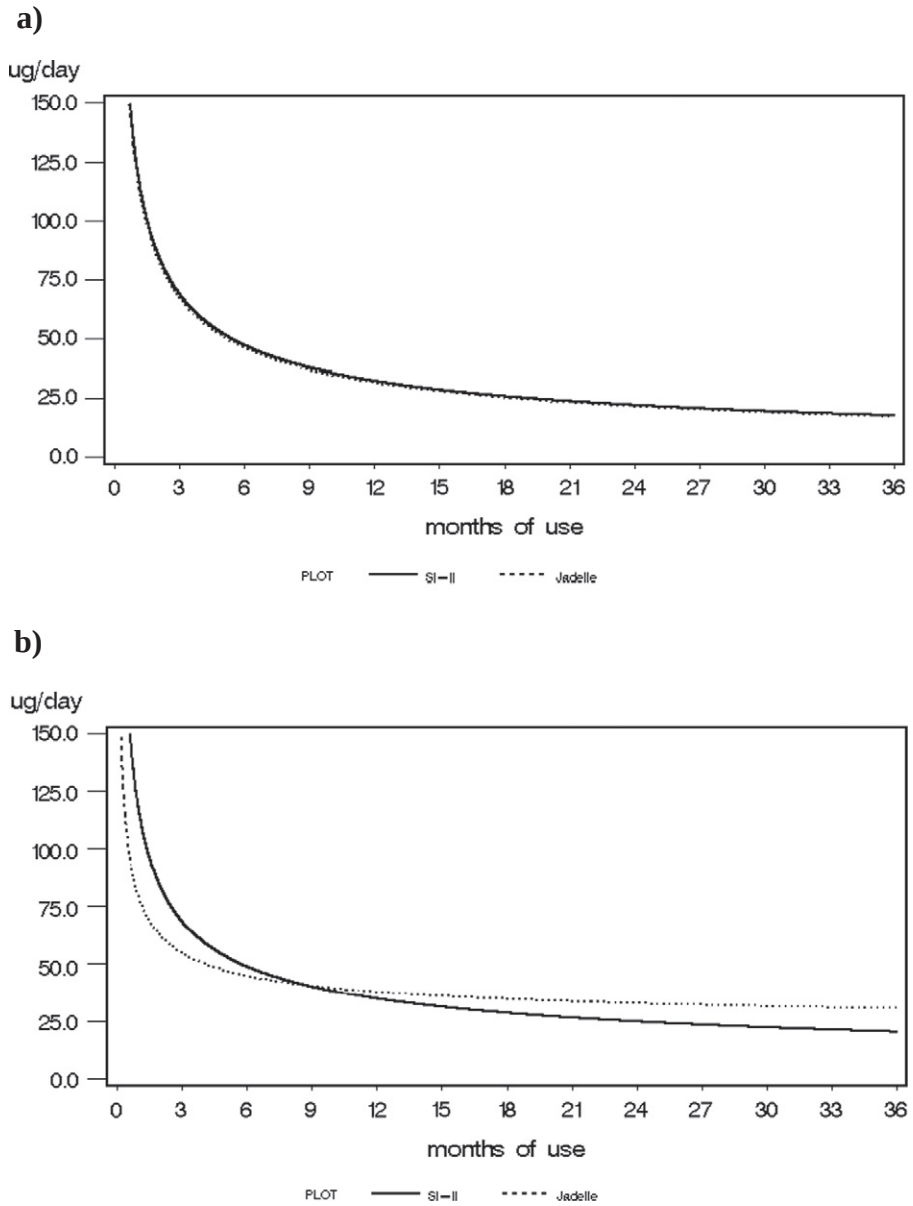

Fig. 2. (a) Predicted daily release rates of LNG using a modified Higuchi model. (S-I (II): dQ/dt = 0.45*1838/days$^{0.55}$; Jadelle: dQ/dt = 0.45*1796/days$^{0.55}$). (b) Predicted daily release rates of LNG using the Population Council model. (S-I (II): dQ/dt = 0.5*1290/days$^{0.5}$ + 0.94; Jadelle: dQ/dt = 0.5*647/days$^{0.5}$ + 20.7).

Higuchi and the Population Council models for estimating LNG release produce comparable results through 2 years. Although the two models diverge somewhat in year 3 with the Population Council model predicting somewhat higher release rates for Jadelle, we believe the assumptions inherent to the modified Higuchi model to be more biologically plausible. The relatively high (80.6) similarity factor, f_2, aligns with the model results indicating similar in vivo release of the two products. In addition to quantitatively describing the similarity of the two dissolution curves, the f_2 is sensitive to large differences in any particular time point [11].

The results of this analysis support findings from clinical trials in China [1] as well as more recent study results indicating that Sino-implant (II) performs as well as Jadelle in the first year of use. Surveillance studies in Bangladesh, Kenya, Pakistan and Madagascar involving more than 2500 women showed first-year pregnancy rates from 0.0% to 0.4% among users of Sino-implant (II) [13–15].

While our findings are reassuring, they should be viewed with caution given several limitations of the analysis. First, we measured LNG release from Sino-implant (II) using a validated assay for the particular product and compared the results to published data for Jadelle. Although we assume that the assay method used with the Jadelle explants was validated for the product, a description of the methods used in the Jadelle analysis is not publically available. We, therefore, cannot rule out possible measurement bias

associated with different laboratory methods used in the two studies. Similarly, the explant data for Sino-implant (II) and Jadelle come from different populations of users, and although we assume that in situ release would not vary by ethnic group or other physical characteristics of the users, such differences could affect results. The analysis is also limited by the relative sparseness of the Sino-implant (II) data and the fact that we had to group the data into 100-day intervals to match the available Jadelle results. We compared data from 24 Sino-implant (II) explants with removal times self-reported by months of use over a period of 3 years to those of 263 Jadelle explants. While the Sino-implant (II) data were sufficient for estimating the f_2 similarity factor, our results would be more robust with additional data points. Finally, the predicted release rates are highly dependent (both in absolute and in relative terms) on which model is fit to the data. While the modified Higuchi and Population Council models produce reasonable results that align with the available observed data, whether or not these are the most appropriate models for release rate data from subdermal implants is currently uncertain. Although our analysis does not meet the full set of guidelines for comparison of in vitro dissolution profiles as described by the European Medicines Agency [4], the results provide evidence of similarity between the two implant systems.

The ongoing 5-year effectiveness study of Sino-implant (II) in the Dominican Republic, which includes 650 women randomized in a 4:1 ratio to either Sino-implant (II) or Jadelle, provides the opportunity to confirm the present study results where the methods are used by the same population over longer use durations. In addition, LNG levels remaining in the explants will be compared to plasma LNG concentrations, which are collected at 6-month intervals and at the time of removal.

Our assessment of in vivo release of LNG from Sino-implant (II) represents an innovative supportive measure for evaluating the similarity of contraceptive effectiveness of long-acting contraceptive methods. After further validation work of this approach, regulatory bodies and WHO's prequalification program could establish guidelines for extended-release methods that include comparative data from explant analyses. Such guidelines could apply in the review of Sino-implant (II) as well as future long-acting contraceptives (or other pharmaceuticals).

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